

Love the One You're with: Vertebrate Guts Shape Their Microbiota

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Using germ-free animals, Rawls et al. (2006) reveal that the gut of a given host can be colonized by the microbiota of another vertebrate. Remarkably, the recipient host then shapes the composition of the non-native microbiota to more closely resemble that of its native consortium.

Of all of the scientific fields that have been impacted by recent technological advances in molecular biology, microbial ecology would have to rank near the top of the list. Biologists now have the ability to identify, and begin to characterize, the functioning of uncultured constituents of complex microbial communities (DeLong and Karl, 2005; Schloss and Handelsman, 2005). Recent explorations using these newly developed approaches have led to the realization that the diversity of all other domains of life pales in comparison to that of the prokaryotes. Over the past decade, the laboratory of Jeffrey Gordon has been a leader in pioneering the study of such microbial communities as they occur in the guts of a vertebrate host. Gordon's group has demonstrated that these communities are in an active dialog with the host, creating a set of interactions that profoundly affects the molecular biology, biochemistry, cell biology, and physiology of the host gut. Underscoring the importance of this notion, systems biologists, most notably Jeremy Nicholson and coworkers, have independently discovered that the gut microbiota are largely responsible for the specific, integrated "metabolic signature" of every human host (Nicholson et al., 2005). Such revelations expose an immense frontier, the exploration of which promises to revolutionize the way in which biologists view the structure and function of the biological world.

With their contribution in this issue of *Cell*, Gordon and his collaborators (Rawls et al., 2006) begin to address a principal question in this developing field: How specific is the composition of the microbial community of the vertebrate gut? In their study they used two phylogenetically divergent hosts, the zebrafish and the mouse. These powerful models of vertebrate biology offer the potential for the eventual discovery of the genetic mechanisms underlying the traits associated with the host-microbe partnerships (Rawls et al., 2004; Bates et al., 2006). To study the composition of the microbial community, they isolated gut microbiota from zebrafish and mouse hosts and performed reciprocal transplantations of these consortia into germ-

free mice and zebrafish, respectively (Figure 1). Gordon's group and others have shown that the divisions of bacteria that comprise the microbiota of the vertebrate gut are a very small subset of the entire array of bacterial divisions (Dethlefsen et al., 2006). Further, they have shown that the normal microbiota of zebrafish and mice share many of these divisions, although marked differences between the zebrafish and mouse microbiota occur at the level of phylo-type (roughly, the species). The central finding of their research reported here is that a vertebrate host can be colonized by the bacterial partners of another vertebrate species, but the ratios and proportions of the shared bacterial divisions will reflect the balance of the divisions natural to

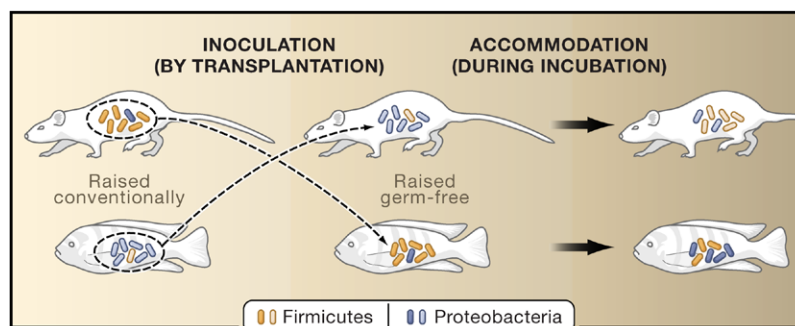


Figure 1. Shaping of the Gut Microbiota by Its Host

In Rawls et al. (2006), the microbiota of conventionally raised mice are introduced into the gut of germ-free zebrafish, and conversely, the microbiota of conventionally raised zebrafish are transplanted into the gut of germ-free mice. Mice and zebrafish naturally have members of the bacterial divisions Firmicutes and Proteobacteria in their gut but have them in different proportions and as distinct phylotypes. When the non-native consortium is introduced into one of these hosts, the host animal appears to promote a higher proportion of the bacterial group that is more abundant in its native consortium.

the host in which the microbiota are residing. Their data demonstrate that the gut environment of a particular host species “selects,” or presents constraints on, which portions of an introduced microbial population will dominate and persist. Taken together, these findings suggest that the gut of a particular vertebrate supports guilds (groups of functionally similar species in the community) (Root, 1967), and that many of these guilds are shared between the gut microbial communities of different vertebrates. By way of analogy one might consider the guild of bread makers within a city; in Paris, the members of this guild share the same niche but would be genetically different and would represent a higher proportion of the overall population than they would in Beijing.

The interactions of the host with its microbial consortium play out through the cell biology and biochemistry of the partners. Rawls et al. explored the functional aspects of these interactions, determining some of the consequences of the colonization of a host with non-native microbiota. Their starting point was the set of lessons learned from their previous microarray studies, which had defined the genomic responses of the zebrafish and mouse to colonization with their native microbiota. Using these data they asked whether similar responses would occur in a host when it is colonized by non-native microbiota. They found that the host animal responded remarkably similarly to a transplanted, “foreign” consortium. That is, the non-native guilds that establish themselves in the mouse or zebrafish gut are capable of eliciting essentially normal responses in the host. Finally, they studied the responses of zebrafish to individual members of the non-native consortium. In many instances, a particular bacterial species, when introduced by itself, would elicit similar responses in both the mouse and zebrafish hosts. Interestingly, they were also able to show that particular components of the microbiota could be assigned to the induction of specific responses in the host, such

as inflammation or cell proliferation.

The work of Gordon’s laboratory that is presented in this contribution, although detailed and extensive, represents only the small tip of a very large iceberg. Within the context of the study itself, several obvious questions arise. Most notable is the issue of whether the non-native consortium that establishes itself in either the mouse or zebrafish is resistant to subsequent displacement by challenge with the native microbiota, that is, what is the resilience of the community? Is possession “nine tenths of the law” in these cases, or is the native microbiota so much more fit that it will naturally assume dominance in such a challenge? The resolution of this issue will provide insight into the specificity of species for their native host. In addition, as Gordon points out, other features of the two gut microenvironments, such as the differences in preferred body temperature and how the temperature is regulated, and/or the disparity in oxygen availability may strongly influence the composition and activity of the microbiota. These factors and others could affect the way these microbes behave in transplantation experiments.

Obtaining answers to these and other related questions will require significant additional research. As this field develops, it will be important to know much more about the natural history of the host animals to ensure that we are studying the natural coevolved associations. For instance, although zebrafish is a well-developed laboratory model, very little information is available about its basic biology (Webb and Schilling, 2006). What, if any, effect has laboratory culture had on the relationship of a model organism with its normal microbiota? Through comparative biology it should be possible to discern how much of the effects Gordon and coworkers observe is due to “fishness” versus “mouseness,” that is, due to the differences that have arisen from their separate evolutionary trajectories, and how much is due to similarities and differences in the lifestyles of these particular spe-

cies. Such analyses would involve the characterizations of in-groups and out-groups within the major vertebrate classes to compare relevant characteristics of the biology of closely related animals with different lifestyles to those of distantly related animals with similar lifestyles.

The importance of the contributions of Gordon and coworkers can hardly be overstated. Biologists have thus far focused principally on the activity of bacteria in two contexts: as constituents of environments such as water or soil and as pathogens. A whole new arena is presented when the natural, healthy environment is the body of an animal or plant. Many insights into this area are coming from studies of human microbiota. The census of the “second human genome project,” which aims to characterize our microbial partners, is now at over 2000 phylotypes of bacteria that persistently associate with each and every human individual. It is important to reflect on the complexity and significance of these relationships compared to those of the 50–100 pathogens that form occasional and often transient associations with only a subset of the human population. Thus, evolutionary theory would likely support the idea that selection on human-microbe interactions is exerted overwhelmingly by the resident microbiota. Although we are approaching an understanding of the quality and quantity of the bacterial presence within humans, many more questions remain to be answered. For example, what is the ratio of resident (coevolved) versus tourist (just passing through) bacteria in any given host; how reproducible are the communities between individual hosts of the same species; what determines community composition and robustness? The questions that have been raised by the newfound awareness of the importance of beneficial host-microbe interactions span all levels of the hierarchy of life, from molecular to ecological. The rigorous study of these interactions will require an influx of talent and expertise and will present new challenges in the training of future biologists.

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The Complex Route to MHC Class I-Peptide Complexes

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The loading of peptides into the groove of MHC class I molecules prior to antigen presentation is a complex process. In this issue of *Cell*, Park et al. (2006) show that peptide loading gets a helping hand from a resident ER enzyme called protein disulfide isomerase, a chaperone that has oxidoreductase activity.

The major histocompatibility complex (MHC) class I molecules are designed to present a peptide signature derived from an intracellular pathogen at the plasma membrane, where it can be detected by cytotoxic T lymphocytes (CTLs). The intracellular processes that participate in bringing about this task include protein degradation, translocation, and folding. In this issue of *Cell*, Ahn and colleagues (Park et al., 2006) add an intriguing new chapter to this complex set of events. These authors describe how the folding of MHC class I molecules is linked to peptide loading by protein disulfide isomerase (PDI), an enzyme in the endoplasmic reticulum (ER). They also show that the US3 protein from human cytomegalovirus has evolved to destroy PDI, thereby obscuring the antigen-presenting function of MHC class I and enabling the virus to evade detection by T cells.

Most peptides presented by MHC class I are derived from cytosolic or nuclear proteins, which are degraded

into fragments by the sequential action of the proteasome and cytosolic peptidases. A few peptides escape complete breakdown into amino acids by binding to chaperones or to a dedicated peptide transporter called TAP that localizes to the ER membrane. The luminal domain of TAP acts as a binding platform for a series of chaperones that support the correct folding of MHC class I in the so-called MHC class I peptide-loading complex (Figure 1A) (Cresswell, 2005). Peptides are translocated into the ER by TAP in a naked form and can then follow different fates. For example, peptides can be trimmed by ER aminopeptidases (sometimes required for generating correct MHC class I binding peptides) or can bind to ER chaperones, albeit with different efficiency. PDI appears to be the most efficient peptide-binding ER chaperone, as it binds to peptides of different length and sequence (Spee et al., 1999). Peptides bound to PDI will be protected from degradation, which may be helpful unless trimming

is required for optimal binding to MHC class I (the optimal size of peptides that bind to MHC class I is usually 9 amino acids). Finally, peptides can be rapidly retrotranslocated into the cytosol. Together, these processes keep the concentration of free peptides low in the ER such that only the most recent peptides in the ER are available for MHC class I binding and do not have to compete with those that arrived earlier (Yewdell et al., 2003). For immunologically relevant peptide presentation, MHC class I has to select high-affinity binding peptides given that they may need to remain at the surface of antigen-presenting cells like dendritic cells for days while they migrate from peripheral tissues to lymph nodes to initiate a T cell response. It is against this background that we are beginning to understand why the loading of MHC class I with high-affinity peptides in the ER turns out to be such a complex business.

The MHC class I molecule is a heterodimer that is stabilized by binding